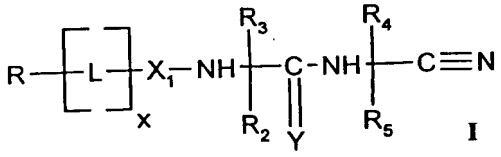
CLAIMS

1. A cathepsin inhibiting pharmaceutical composition comprising a dipeptide nitrile in which the C-terminal carboxy group of the dipeptide is replaced by a nitrile group (-C≡N) and in which the N-terminal nitrogen atom is substituted via a peptide or pseudopeptide linkage which optionally additionally comprises a -methylene-hetero atom- linker or an additional hetero atom, directly by aryl, lower alkyl, lower alkenyl, lower alkynyl or heterocyclyl or a physiologically-acceptable and -cleavable ester or a salt thereof, in combination with a pharmaceutically acceptable carrier.

2. A cathepsin inhibiting pharmaceutical composition according to claim 1 comprising a compound of formula I, or a physiologically-acceptable and -cleavable ester or a salt thereof



I

wherein:

R is optionally substituted (aryl, lower alkyl, lower alkenyl, lower alkynyl, or heterocyclyl);

R_2 and R_3 are independently hydrogen, or optionally substituted [lower alkyl, cycloalkyl, bicycloalkyl, or (aryl, biaryl, cycloalkyl or bicycloalkyl)-lower alkyl]; or

R_2 and R_3 together represent lower alkylene, optionally interrupted by O, S or NR_6, so as to form a ring with the carbon atom to which they are attached

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl; or

either R_2 or R_3 are linked by lower alkylene to the adjacent nitrogen to form a ring;

R_4 and R_5 are independently H, or optionally substituted (lower alkyl, aryl-lower alkyl), -$C(O)OR_7$, or -$C(O)NR_7R_8$,

wherein

R_7 is optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl or heterocyclyl), and

R_8 is H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl or heterocyclyl), or

R_4 and R_5 together represent lower alkylene, optionally interrupted by O, S or NR_6, so as to form a ring with the carbon atom to which they are attached

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl, or

R_4 is H or optionally substituted lower alkyl and R_5 is a substituent of formula $-X_2-(Y_1)_n-(Ar)_p-Q-Z$

wherein

Y_1 is O, S, SO, SO_2, $N(R_6)SO_2$, $N-R_6$, SO_2NR_6, $CONR_6$ or NR_6CO;

n is zero or one;

p is zero or one;

X_2 is lower alkylene; or when n is zero, X_2 is also C_2-C_7-alkylene interrupted by O, S, SO, SO_2, NR_6, SO_2NR_6, $CONR_6$ or NR_6CO;

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl;

Ar is arylene;

Z is hydroxy, acyloxy, carboxyl, esterified carboxyl, amidated carboxyl, aminosulfonyl, (lower alkyl or aryl-lower alkyl)aminosulfonyl, or (lower alkyl or aryl-lower alkyl)sulfonylaminocarbonyl; or Z is tetrazolyl, triazolyl or imidazolyl;

Q is a direct bond, lower alkylene, Y_1-lower alkylene or C_2-C_7-alkylene interrupted by Y_1;

X_1 is $-C(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, or $-P(O)(OR_6)-$,

wherein R_6 is as defined above;

Y is oxygen or sulphur;

L is optionally substituted -Het-, $-Het-CH_2-$ or $-CH_2-Het-$,

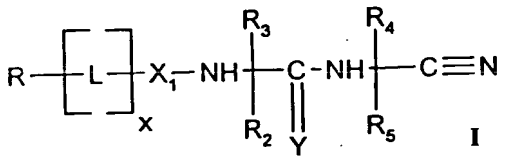
wherein Het is a hetero atom selected from O, N or S, and

x is zero or one;

and aryl in the above definitions represents carbocyclic or heterocyclic aryl;

in combination with a pharmaceutically acceptable carrier.

3. A compound of formula I, or a physiologically-acceptable and -cleavable ester or a salt thereof



I

wherein:

R is optionally substituted (aryl, lower alkyl, lower alkenyl, lower alkynyl, or heterocyclyl);

R_2 and R_3 are independently hydrogen, or optionally substituted [lower alkyl, cycloalkyl, bicycloalkyl, or (aryl, biaryl, cycloalkyl or bicycloalkyl)-lower alkyl]; or

R_2 and R_3 together represent lower alkylene, optionally interrupted by O, S or NR_6, so as to form a ring with the carbon atom to which they are attached

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl; or

either R_2 or R_3 are linked by lower alkylene to the adjacent nitrogen to form a ring;

R_4 and R_5 are independently H, or optionally substituted (lower alkyl, aryl-lower alkyl), -$C(O)OR_7$, or -$C(O)NR_7R_8$,

wherein

R_7 is optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl or heterocyclyl), and

R_8 is H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, cycloalkyl, bicycloalkyl or heterocyclyl), or

R_4 and R_5 together represent lower alkylene, optionally interrupted by O, S or NR_6, so as to form a ring with the carbon atom to which they are attached

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl, or

R_4 is H or optionally substituted lower alkyl and R_5 is a substituent of formula -X_2-$(Y_1)_n$-$(Ar)_p$-Q-Z

wherein

Y_1 is O, S, SO, SO_2, $N(R_6)SO_2$, N-R_6, SO_2NR_6, $CONR_6$ or NR_6CO;

n is zero or one;

p is zero or one;

X_2 is lower alkylene; or when n is zero, X_2 is also C_2-C_7-alkylene interrupted by O, S, SO, SO_2, NR_6, SO_2NR_6, $CONR_6$ or NR_6CO;

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl;

Ar is arylene;

Z is hydroxy, acyloxy, carboxyl, esterified carboxyl, amidated carboxyl, aminosulfonyl, (lower alkyl or aryl-lower alkyl)aminosulfonyl, or (lower alkyl or aryl-lower alkyl)sulfonylaminocarbonyl; or Z is tetrazolyl, triazolyl or imidazolyl;

Q is a direct bond, lower alkylene, Y_1-lower alkylene or C_2-C_7-alkylene interrupted by Y_1;

X_1 is -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$-, or $-P(O)(OR_6)$-,

wherein R_6 is as defined above;

Y is oxygen or sulphur;

L is optionally substituted -Het-, -Het-CH_2- or -CH_2-Het-,

wherein Het is a hetero atom selected from O, N or S, and

x is zero or one;

and aryl in the above definitions represents carbocyclic or heterocyclic aryl;

provided that when R is lower alkyl not substituted by aryl,

one of R_4 or R_5 is a substituent of formula $-X_2-(Y_1)_n-(Ar)_p-Q-Z$;

provided that when x is one, L is -O-, or -CH_2-O- and X_1 is -C(O)-,

either one of R_4 or R_5 is a substituent of formula $-X_2-(Y_1)_n-(Ar)_p-Q-Z$, or R is not unsubstituted phenyl;

provided that when $R_2 = R_4 = R_5 = H$, x is zero and X_1 is -C(O)-,

R_3 is not H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH-(CH_3)_2$, $-CH_2-COOH$, or $-CH_2-COO-CH_2-CH_3$,

when R is unsubstituted phenyl,

R_3 is not H, $-CH(CH_3)_2$, or $-CH_2-CH-(CH_3)_2$, when R is 4-aminophenyl or 4-nitrophenyl,

R_3 is not H when R is 3-aminophenyl, 3-nitrophenyl 2-chloropyridin-4-yl, or vinyl or

R_3 is not $-CH_2-CH_2-S-CH_3$ when R is pyridin-3-yl or 2-chloropyridin-4-yl,

provided that when $R_2 = R_3 = R_4 = H$, x is zero and X_1 is -C(O)- and R is phenyl,

R_5 is not $-CH(CH_3)_2$,

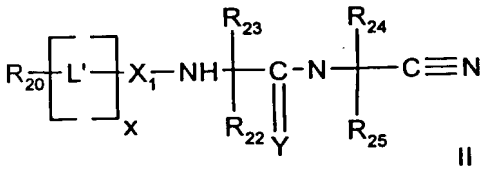
provided that when $R_3 = R_4 = H$, R_5 is $-CH_2-CH_2-COOH$, x is zero and X_1 is -C(O)-,

R_2 does not form a heterocyclic ring with the adjacent nitrogen atom, and

provided that when $R_2 = R_3 = R_4 = R_5 = H$, x is zero and X_1 is $-SO_2-$,

R is not 4-methylphenyl.

4. A compound according to claim 3, of formula II, or a physiologically-acceptable and -cleavable ester or a salt thereof



II

wherein:

R_{20} is optionally substituted (aryl, aryl-lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl, or heterocyclyl-lower alkyl);

R_{22} is H, or optionally substitued lower alkyl, and

R_{23} is optionally substituted (lower alkyl, aryl-lower alkyl, or cyloalkyl-lower alkyl) or

R_{22} and R_{23} together with the carbon atom to which they are attached form an optionally substituted (cycloalkyl group or heterocycloalkyl group);

R_{24} and R_{25} are independently H, or optionally substituted (lower alkyl, or aryl-lower alkyl), $-C(O)OR_7$, or $-C(O)NR_7R_8$,

wherein R_7 and R_8 are as defined above, or

R_{24} and R_{25} together with the carbon atom to which they are attached form an optionally substituted (cycloalkyl group or heterocycloalkyl group);

X_1 is as defined in claim 2;

Y is oxygen or sulphur;

L' is optionally substituted (-Het-CH_2- or -CH_2-Het-),

wherein Het is a a hetero atom selected from O, N or S, and

x is 1 or 0,

provided that when x is one, L is -CH_2-O- and X_1 is -C(O)-,

R_{20} is not unsubstituted phenyl,

provided that when $R_{22} = R_{24} = R_{25} = H$, x is zero and X_1 is -C(O)-,

R_{23} is not H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH-(CH_3)_2$, $-CH_2-COOH$, or $-CH_2-COO-CH_2-CH_3$, when R_{20} is unsubstituted phenyl,

R_{23} is not H, $-CH(CH_3)_2$, or $-CH_2-CH-(CH_3)_2$, when R_{20} is 4-aminophenyl or 4-nitrophenyl,

R_{23} is not H when R_{20} is 3-aminophenyl, 3-nitrophenyl 2-chloropyridin-4-yl, or vinyl, or

R_{23} is not $-CH_2-CH_2-S-CH_3$ when R_{20} is pyridin-3-yl or 2-chloropyridin-4-yl,

provided that when $R_{22} = R_{23} = R_{24} = H$, x is zero and X_1 is -C(O)- and R_{20} is phenyl,

R_{25} is not $-CH(CH_3)_2$,

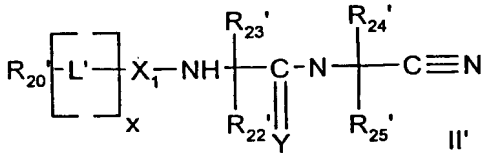
provided that when $R_{23} = R_{24} = H$, R_{25} is $-CH_2-CH_2-COOH$, x is zero and X_1 is -C(O)-,

R_{22} does not form a heterocyclic ring with the adjacent nitrogen atom, and

provided that when $R_{22} = R_{23} = R_{24} = R_{25} = H$, x is zero and X_1 is $-SO_2-$,

R_{20} is not 4-methylphenyl.

5. A compound according to claim 3, of formula II' or a physiologically-acceptable and -cleavable ester or a salt thereof



II'

wherein:

R_{20}' is optionally substituted (C_6-C_{18} aryl or C_4-C_{18} heteroaryl);

R_{22}' is H, or optionally substitued C_1-C_8 alkyl, and

R_{23}' is optionally substituted (C_2-C_8 alkyl, or C_7-C_{14} aralkyl), or

R_{22}' and R_{23}' together with the carbon atom to which they are attached form an optionally substituted (C_3-C_8 cycloalkyl group or C_4-C_7 heterocycloalkyl group);

R_{24}' and R_{25}' are independently H, or optionally substituted (C_1-C_8 alkyl, C_7-C_{14} aralkyl, or C_5-C_{14} heteroaralkyl), $-C(O)OR_6$', or $-C(O)NR_6'R_7'$,

wherein

R_6' is optionally substituted (C_1-C_8 alkyl, C_7-C_{14} aralkyl, C_3-C_8 cycloalkyl, C_4-C_7 heterocycloalkyl, C_5-C_{14} heteroaralkyl, C_6-C_{14} aryl, or C_4-C_{14} heteroaryl), and

R_7' is H, or optionally substituted (C_1-C_8 alkyl, C_7-C_{14} aralkyl, C_3-C_8 cycloalkyl, C_4-C_7 heterocycloalkyl, C_5-C_{14} heteroaralkyl, C_6-C_{14} aryl, or C_4-C_{14} heteroaryl), or

R_{24}' and R_{25}' together with the carbon atom to which they are attached form an optionally substituted (C_3-C_8 cycloalkyl group or C_4-C_7 heterocycloalkyl group);

X_1 is -C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -P(O)(OR_6')-

wherein R_6' is as defined above;

Y is oxygen or sulphur;

L' is optionally substituted (-Het-CH_2- or -CH_2-Het-),

wherein Het is a a hetero atom selected from O, N or S, and

x is 1 or 0,

provided that when x is one, L' is -CH_2-O- and X_1 is -C(O)-

R_{20}' is not unsubstituted phenyl,

provided that when R_{22}' = R_{24}' = R_{25}' = H, x is zero and X_1 is -C(O)-,

R_{23}' is not H, -CH_3, -$CH(CH_3)_2$, -CH_2-CH-$(CH_3)_2$, -CH_2-COOH, or -CH_2-COO-CH_2-CH_3, when R_{20}' is unsubstituted phenyl,

R_{23}' is not H, -$CH(CH_3)_2$, or -CH_2-CH-$(CH_3)_2$, when R_{20}' is 4-aminophenyl or 4-nitrophenyl,

R_{23}' is not H when R_{20}' is 3-aminophenyl, 3-nitrophenyl, 2-chloropyridin-4-yl, or vinyl, or

R_{23}' is not -CH_2-CH_2-S-CH_3 when R_{20}' is pyridin-3-yl or 2-chloropyridin-4-yl,

provided that when R_{22}' = R_{23}' = R_{24}' = H, x is zero and X_1 is -C(O)- and R_{20}' is phenyl,

R_{25}' is not -$CH(CH_3)_2$,

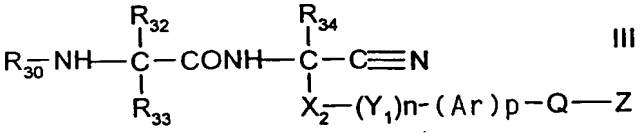
provided that when R_{23}' = R_{24}' = H, R_{25}' is -CH_2-CH_2-COOH, x is zero and X_1 is -C(O)-,

R_{20}' does not form a heterocyclic ring with the adjacent nitrogen atom, and

provided that when R_{22}' = R_{23}' = R_{24}' = R_{25}' H, x is zero and X_1 is -SO_2-,

R_{20}' is not 4-methylphenyl.

6. A cathepsin inhibiting pharmaceutical composition comprising a compound of formula III



III

wherein

R_{30} is an acyl group derived from an organic carboxylic, carbonic, carbamic or sulfonic acid;

R_{32} and R_{33} are independently hydrogen, lower alkyl, cycloalkyl, bicycloalkyl, or (aryl, biaryl, cycloalkyl or bicycloalkyl)-lower alkyl; or R_{32} and R_{33} together represent lower alkylene so as to form a ring together with the carbon to which they are attached;

R_{34} is hydrogen or lower alkyl;

Y_1 is O, S, SO, SO_2, $N(R_6)SO_2$, N-R_6, SO_2NR_6, $CONR_6$ or NR_6CO;

n is zero or one;

p is zero or one;

X_2 is lower alkylene; or when n is zero, X_2 is also C_2-C_7-alkylene interrupted by O, S, SO, SO_2, NR_6, SO_2NR_6, $CONR_6$ or NR_6CO;

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl;

Ar is arylene;

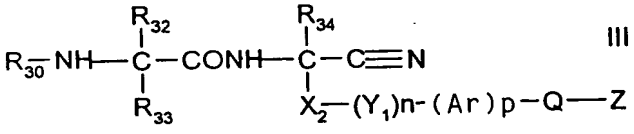
Z is hydroxy, acyloxy, carboxyl, esterified carboxyl, amidated carboxyl, aminosulfonyl, (lower alkyl or aryl-lower alkyl)aminosulfonyl, or (lower alkyl or aryl-lower alkyl)sulfonylaminocarbonyl; or Z is tetrazolyl, triazolyl or imidazolyl;

Q is a direct bond, lower alkylene, Y_1-lower alkylene or C_2-C_7-alkylene interrupted by Y_1;

or a pharmaceutically acceptable salt or ester thereof;

in combination with a pharmaceutically acceptable carrier.

7. A compound of formula III



III

wherein

R_{30} is an acyl group derived from an organic carboxylic, carbamic or sulfonic acid;

R_{32} and R_{33} are independently hydrogen, lower alkyl, cycloalkyl, bicycloalkyl, or (aryl, biaryl, cycloalkyl or bicycloalkyl)-lower alkyl; or R_{32} and R_{33} together represent lower alkylene

so as to form a ring together with the carbon to which they are attached;

R_{34} is hydrogen or lower alkyl;

Y_1 is O, S, SO, SO_2, $N(R_6)SO_2$, N-R_6, SO_2NR_6, $CONR_6$ or NR_6CO;

n is zero or one;

p is zero or one;

X_2 is lower alkylene; or when n is zero, X_2 is also C_2-C_7-alkylene interrupted by O, S, SO, SO_2, NR_6, SO_2NR_6, $CONR_6$ or NR_6CO;

wherein R_6 is hydrogen, lower alkyl or aryl-lower alkyl;

Ar is arylene;

Z is hydroxy, acyloxy, carboxyl, esterified carboxyl, amidated carboxyl, aminosulfonyl, (lower alkyl or aryl-lower alkyl)aminosulfonyl, or (lower alkyl or aryl-lower alkyl)sulfonylaminocarbonyl; or Z is tetrazolyl, triazolyl or imidazolyl;

Q is a direct bond, lower alkylene, Y_1-lower alkylene or C_2-C_7-alkylene interrupted by Y_1;

or a pharmaceutically acceptable salt or ester thereof.

8. A compound according to claim 7, wherein

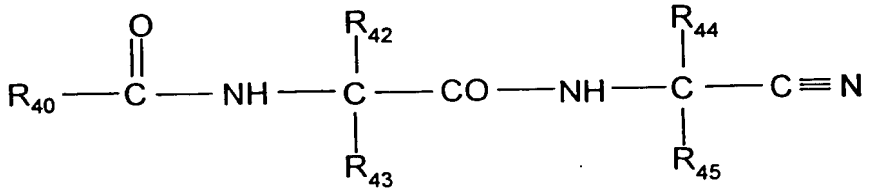
(a) p is one;

(b) Y_1 is O, S, SO, SO_2, $N(R_6)SO_2$ or N-R_6; and

(c) X_2 is lower alkylene; or when n is zero, X_2 is also C_2-C_7-alkylene interrupted by O, S, SO, SO_2 or NR_6,

or a pharmaceutically acceptable salt or ester thereof.

9. A compound according to claim 3, of formula IV



(IV)

wherein

R_{40} is substituted phenyl or heterocyclic aryl, (mono- or di- carbocyclic or heterocyclic aryl)-lower alkyl or lower alkenyl, or heterocyclyl;

R_{42} is hydrogen or lower alkyl;

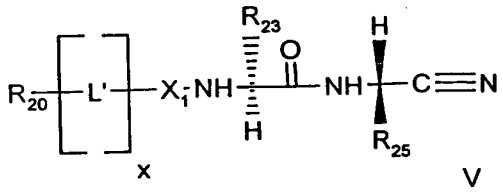
R_{43} is carbocyclic or heterocyclic aryl - lower alkyl;

R_{44} and R_{45} are independently hydrogen or lower alkyl; or

R_{44} and R_{45} combined represent lower alkylene;

or a pharmaceutically acceptable salt or esters thereof.

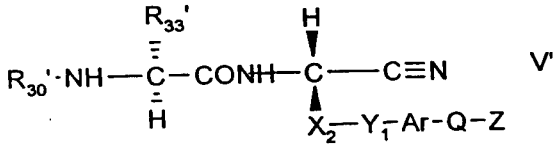
10. A compound according to claim 4 of the formula V,



V

wherein the symbols are as defined in said claim, or a physiologically-acceptable and -cleavable ester or salt thereof.

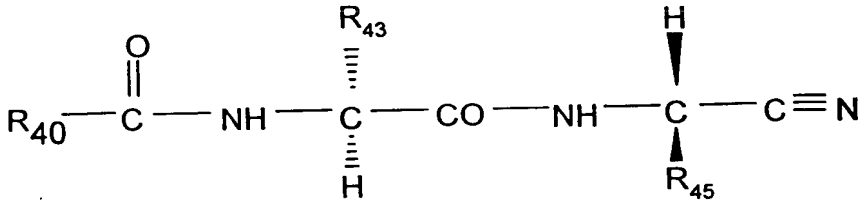
11. A compound according to claim 7 of the formula V'



V'

wherein the symbols are as defined in said claim, or a physiologically-acceptable and -cleavable ester or salt thereof.

12. A compound according to claim 9 of the formula V"

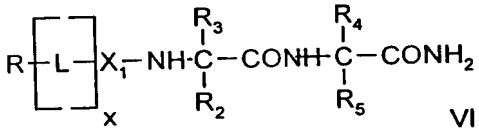


V"

wherein the symbols are as defined in said claim, or a physiologically-acceptable and -cleavable ester or salt thereof.

13. A process for the preparation of a compound of formula I as defined in claim 3, comprising

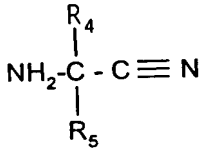
(a) converting an amide of the formula VI



VI

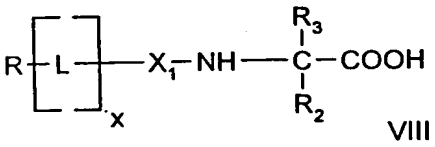
wherein R, R_2, R_3, R_4 and R_5 have meaning as previously defined in claim 2 for the compounds of formula I to a nitrile of formula I; or

(b) condensing a compound of the formula VII



VII

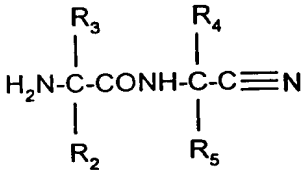
wherein R_4 and R_5 have meaning as defined in claim 1, with an acid of formula VIII



VIII

wherein R, R_2 and R_3 have meaning as defined in claim 1; or with a reactive derivative thereof; or

(c) condensing a compound of the formula Ia



(Ia)

wherein R_2, R_3, R_4 and R_5 have meaning as defined in claim 1 with an acid corresponding to the group $R-[L]_x-X_1-$ or with a reactive derivative thereof; and in the above processes, if required, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting any resulting compound into another compound of the invention; and/or if desired, converting a resulting compound into a salt or a resulting salt into the free acid or base or into another salt.

14. A method of inhibiting cathepsin activity in a mammal which comprises administering to a mammal in need thereof an effective amount of a pharmaceutical composition as defined in claim 1.

15. A method of inhibiting cathepsin activity in a mammal which comprises administering to a mammal in need thereof an effective amount of a pharmaceutical composition as defined in claim 2.

16. A method of inhibiting cathepsin activity in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of formula I as defined in claim 3.

17. A method of treating cathepsin dependent conditions in a mammal which comprises administering to a mammal in need thereof an effective amount of a pharmaceutical composition as defined in claim 2.

18. A method according to claim 17 of treating inflammation, osteoporosis, rheumatoid arthritis and osteoarthritis.

19. A method of treating cathepsin dependent conditions in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound as defined in claim 3.

20. A cathepsin inhibiting pharmaceutical composition comprising a compound of formula I as defined in claim 3, in combination with a pharmaceutically acceptable carrier.